Biomedical Science

Cytokines and Reproduction

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Cytokines are important in reproduction. Interleukin-1, an established immune mediator, is one of the best-characterized members of the cytokine family. We describe what is known about the interactions between the interleukin-1 system and the hypothalamic-pituitary-gonadal, the hypothalamic pituitary-adrenal, and the hypothalamic-pituitary-thyroid axes. We also review the ovarian role of the interleukin-1 system. This cytokine has an immense and, as yet, imperfectly understood effect on the human reproductive tract. Clearly the immune system has a potential autocrine, paracrine, and endocrine role in regulating human reproductive events such as ovulation, luteinization, and implantation.

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For many years investigators and clinicians have attempted to understand the complexity of the human reproductive process. Anatomy, embryology, endocrinology, and other disciplines have been involved, but important questions remain unanswered. Recently a new immunologic approach to understanding the reproductive process appears to be illuminating.

Clinical and experimental evidence indicates that immune reactivity is greater in females than in males.[1] This condition provides females with an increased resistance to a variety of infections.[2] But women also have a much higher incidence of certain autoimmune diseases such as thyroid autoimmune diseases and systemic lupus erythematosus during the reproductive years.[3] These observations strongly suggest that the reproductive system plays an important role in the regulation of the immune system. Conversely, advances in the basic understanding of the immune system have provided new insights about the relevance of immune mediators in the reproductive system.[4] In particular, polypeptides produced by lymphocytes and monocytes, which were originally called lymphokines and monokines, respectively, are now known to be produced in various tissues other than leukocytes. They have also been found to have a broad spectrum of normal and disease-related actions on the reproductive system in addition to the regulation of immune functions.[5] The more generic term, cytokine, has replaced the terms lymphokine and monokine in common use.

The catalog of cytokines is still expanding. It includes interleukins 1 to 13 (IL-1 to -13), tumor necrosis factor α and β, transforming growth factor β, interferon α, β, and γ, leukocyte inhibitory factor, and colony-stimulating factor 1. All of these factors are polypeptides and act on a variety of target cells through specific plasma membrane receptor proteins[6] in a non-antigen-specific manner. A typical action is defined as autocrine or paracrine (feedback action on the cell that produces the cytokine or action on the surrounding cells), but not commonly considered endocrine. In this review, we present evidence of IL-1 endocrine actions.

Interleukin-1 System

The introduction of a foreign stimulus elicits a complex response that must have evolved to protect persons from the invasion of substances from outside the self.[7] Interleukin-1 is one of the earliest, if not the first, cytokine produced by macrophages or monocytes in response to these stimuli and is essential for the immune cascade. Interleukin-1 is not produced exclusively by cells of the immune system; rather, it is also a product of many cell types, such as fibroblasts and epithelial cells. Furthermore, its effects are not restricted to leukocytes but are manifested in other cells of various tissues modulating immune, neuroendocrine, and metabolic functions.[8]

Interleukin-1 is a family composed of three structurally related polypeptides. Two are agonists: interleukin-1α (IL-1α) and interleukin-1β (IL-1β), and one is an inhibitor, interleukin-1 receptor antagonist (Figure 1). Although the genes for IL-1α and IL-1β are different and located on separate areas of chromosome 2, both recognize the same receptor on target cells and produce similar biologic effects.[9] Molecular cloning of IL-1α and IL-1β genes has revealed a nucleic acid homology of 45% and a surprisingly low amino acid homology of only 26%; in addition, both molecules have distinct isoelectric points (pI 5 and 7, respectively). The primary amino acid sequence of mature IL-1β is conserved among the various animal species in the range of 75% to 78%, whereas the α-sequence is conserved in the range of 60% to 70%.[8] In addition, IL-1α and IL-1β genes are differentially expressed in various tissues.[10] The two forms of IL-1 are initially synthesized as intracytoplasmic 31-kd precursors.

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ABBREVIATIONS USED IN TEXT

CRH = corticotropin-releasing hormone
FSH = follicle-stimulating hormone
HPA = hypothalamic-pituitary-adrenal
IL-1 = interleukin-1
LH = luteinizing hormone
mRNA = messenger RNA
TSH = thyroid-stimulating hormone

The precursor to IL-1 is cleaved by IL-1β converting enzyme,[11] generating a carboxyl-terminal 17-kd peptide called "mature" IL-1β that is the biologically active form and is released by the cell to the extracellular space and the circulation. The IL-1α precursor is transported to the cell surface and anchored to the plasma membrane. Unlike the IL-1β precursor, the IL-1α precursor is biologically active. Finally, IL-1 precursors are cleaved to yield mature molecules of 159 amino acids (IL-1α) and 153 amino acids (IL-1β) when released from the cells.

The IL-1 receptor antagonist is another polypeptide that competes with IL-1α and -β for IL-1 surface receptor occupancy.[12] It is a specific inhibitor of interleukin-1 activity that acts by blocking the binding of IL-1 to its cell surface receptors.[13] This remarkable difference is important for cytokine biology. The complementary DNA for the IL-1 receptor antagonist encodes a 152-amino acid protein, which shows a striking similarity with IL-1α and IL-1β molecules. This molecule provides some protection against the manifestations of disease provoked by IL-1. Further evidence of relevancy is provided by studies that have shown that IL-1 receptor antagonist is synthesized in animals with sepsis and reduces the severity of septic shock and colitis induced by IL-1.[14,15] Preliminary clinical studies suggest that IL-1 receptor antagonist may be beneficial in patients with sepsis.[16]

There are two IL-1 receptors, now indicated as IL-1 receptor type I and type II, and corresponding to the 80-kd and 68-kd IL-1 binding proteins on the plasma membranes of T and B cells, respectively.[17,18] Both are members of the immunoglobulin superfamily, and they are structurally related to each other. The type I receptor is found primarily on T cells, whereas the type II receptor is found on neutrophils, B cells, and bone marrow cells. Some cells, however, such as monocytes, probably express both types, and both may cooperate in binding and signal transduction. Interleukin-1α has a higher affinity for the type I receptor, whereas IL-1β has a greater affinity for the type II receptor. Nonetheless, both receptors recognize the α and β forms of IL-1. The receptor antagonist of IL-1 recognizes the type I receptor, but information regarding its affinity for the type II receptor is unclear. Also, a natural soluble form of IL-1 receptor has been identified in body fluids.[19] This soluble receptor is generated by proteolytic cleavage of the extracellular portion of the type II receptor. A general feature of receptor-ligand interactions is the internalization of the complex by receptor-mediated endocytosis.[20] Presumably when the two IL-1 receptor types are present in the same cell, they function independently at the level of ligand binding and do not form a heterodimeric receptor complex.[21] There is still no clear consensus regarding the role of classical second messengers in IL-1 action; what appears certain is that in EL4 cells, IL-1β signals through the sphingomyelin pathway.[22]

Interactions Between the Interleukin-1 System and the Hypothalamic-Pituitary-Gonadal Axis

Infection and inflammation are usually accompanied by a central inhibition of reproductive function, as in patients with sepsis and burns, for example. Interleukin-1 has been reported to be produced by central neurons, glial cells, and brain macrophages.[23-25] It has also been shown that the hypothalamus and hippocampal neurons contain a high density of IL-1 receptor type I.[26] To elucidate the mechanism whereby IL-1 may be involved in the regulation of the hypothalamic-pituitary-gonadal axis, several authors have studied the effect of IL-1α and IL-1β on the rat hypothalamic-pituitary-gonadal axis in vivo and in vitro (Figure 2).[27-29] Their results suggest that the intracerebroventricular administration of IL-1 acts at the central level by inhibiting the release of both gonadotropin-releasing hormone and luteinizing hormone (LH), with a specificity sufficient to exclude an effect on the secretion of follicle-stimulating hormone (FSH).[30] In normal human subjects, plasma concentrations of IL-1β are usually below the level of detection, except in women after ovulation[31] or in subjects after strenuous exercise. In patients with burns and sepsis, increased plasma levels of IL-1β are frequently associated with reduced LH and testosterone levels.[32,33] Also, the capability of IL-1 to increase the pituitary secretion of prolactin and growth hormone in patients with acute immune reactions has been demonstrated.[34] Prolactin is required for the normal maintenance of lymphoid tissues and immune responses of macrophages and T and B cells in rodents.[35] The inhibition of the pituitary release of prolactin by bromocriptine administration in rats selectively reduces lymphocyte reactivity in vitro and in vivo, whereas the immune deficiency of hypophysectomized rats is reversed by pro-

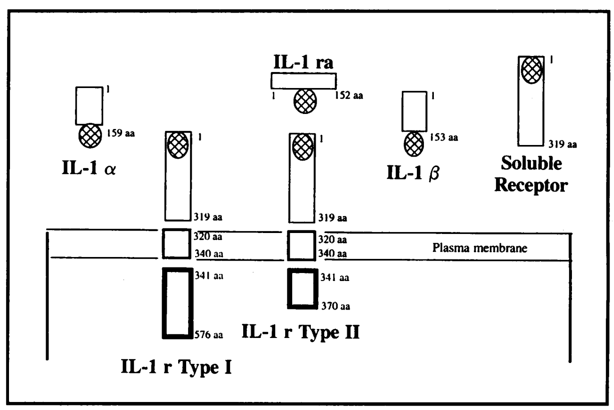

Figure 1.—The diagram shows the interleukin-1 (IL-1) family. Circles represent the receptor site that is shared by all the members of the family. aa = amino acid numbers; IL-1 ra = interleukin-1 receptor antagonist; IL-1 r type I, type II = interleukin-1 receptor type I, type II

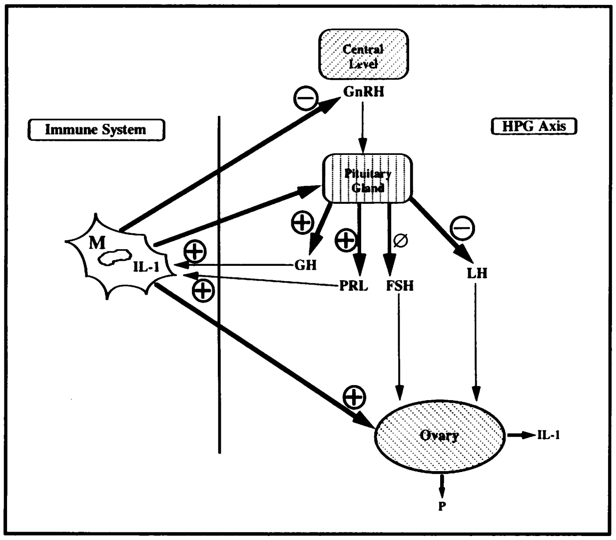

Figure 2.—The diagram represents the interactions between interleukin-1 (IL-1) and the hypothalamic-pituitary-gonadal (HPG) axis. FSH = follicle-stimulating hormone, GH = growth hormone, GnRH = gonadotropin-releasing hormone, LH = luteinizing hormone, M = macrophages, P = progesterone, PRL = prolactin, ➡ = effects produced by IL-1 on hormonal regulation, → = effects produced by hormones on IL-1 regulation, + = stimulatory effect, − = inhibitory effect, ∅ = no effect

lactin, placental lactogen, or growth hormone, but not other pituitary hormones.[36]

The IL-1 system also acts at the level of the gonads. Previous studies have established in pigs,[37,38] mice,[39,40] hamsters,[41] and humans[42] that the ovaries are the site for IL-1 reception and action. In these animal models, IL-1 imparts potent antigonadotropic[37-40] or steroidogenic[41] effects under various experimental conditions. In humans, this steroidogenic effect is controversial. Both human peripheral blood monocytes and peritoneal macrophages have been shown to be capable of stimulating progesterone production by granulosa-lutein cells.[43] Although IL-1β is the likely candidate for this stimulatory effect, the action of IL-1β or IL-1α on either basal or human chorionic gonadotropin-stimulated estradiol or progesterone production by cultured human granulosa-lutein cells remains controversial and may depend on specific culture conditions and IL-1 preparations. Also relevant to granulosa cell differentiation is the finding that the number of LH receptors induced by FSH is inhibited by IL-1 in rat granulosa cells,[39,40] and this inhibition of LH receptor development by IL-1β is dose-dependent and time-related.[40]

Not only does IL-1 modulate steroid and gonadotropin secretion, but gonadotropins and gonadal steroids, in turn, have been shown to interact with the immune system and modulate the secretion of IL-1. There are several explanations for this surprising hormonal regulation of the immune response:

• Human lymphocytes secrete immunoreactive and bioactive LH, FSH, or human chorionic gonadotropin.[44,45]

• The presence of LH-releasing hormone receptors on porcine lymphocytes has been demonstrated,[46] suggesting that gonadotropin production by lymphocytes may be triggered by gonadotropin-releasing hormone.

• Gonadotropins regulate IL-1 messenger RNA (mRNA) expression in various cell types other than hematopoietic cells. In fact, the gonadotropin-dependent preovulatory induction of IL-1 transcripts in the theca-interstitial cell layer in murine[47] and human[42] ovaries specifically implicates the IL-1 system in the preovulatory cascade. Furthermore, an ovulatory effect of IL-1 has been documented in vitro in perfused rat ovaries[48] and in perfused rabbit ovaries.[49] These results suggest an autocrine-paracrine action of IL-1 in the ovary, especially during ovulation.

• Human monocyte production of IL-1β is regulated by gonadal steroids. We have shown that cultured peripheral monocytes isolated during the late luteal phase secrete substantially higher levels of IL-1β than cultured monocytes isolated during the preovulatory follicular phase.[50] In addition, low levels (10^{-9} mol per liter) of the gonadal steroids, estradiol (E_2) and progesterone, may stimulate, and at higher levels ($\geq 10^{-7}$ mol per liter) substantially inhibit, IL-1 activity[51] and IL-1β mRNA levels[52] of both peripheral monocytes and placental macrophages. Also, estradiol modulates IL-1 production by macrophages.[53] This correlation is supported by the reduced synthesis of IL-1 by macrophages in rats whose ovaries were removed and an increment in IL-1 synthesis after estradiol replacement in vivo and in vitro.[53] These results together suggest a hormonal regulation of IL-1 production. This remarkable endocrine feedback regulation between IL-1 and ovarian steroids may be another regulatory loop important for the ovulation or luteinization processes.

Multiple autocrine-paracrine-endocrine loops exist between the immune and reproductive systems, further suggesting a remarkable feedback regulation between them that controls ovulation, luteinization, or both.

Interactions Between the Interleukin-1 System and the Hypothalamic-Pituitary-Adrenal Axis

Hormones produced by the adrenal gland have important effects on the reproductive system. Hyperfunction and hypofunction of the adrenal gland result in chronic anovulation and amenorrhea.

The IL-1 system activates the hypothalamic-pituitary-adrenal (HPA) axis at different levels (Figure 3). Intravenous or intracerebroventricular administration of IL-1 produces a prompt rise in corticotropin-releasing hormone (CRH) release at the hypothalamic level, leading to increased plasma levels of adrenocorticotropin, or corticotropin, within 30 minutes after administration. Direct effects on the pituitary corticotrophs are not as clear; however, a stimulatory effect by IL-1 on corticotropin secretion from human pituitary adenoma cells has been reported. Corticotropin-releasing hormone receptors exist in peripheral sites of the immune system, and CRH directly stimulates leukocytes to produce IL-1. Finally, cytokines including IL-1 also act directly on the adrenal cortex to enhance prostaglandin E_2 production and corticosterone re-

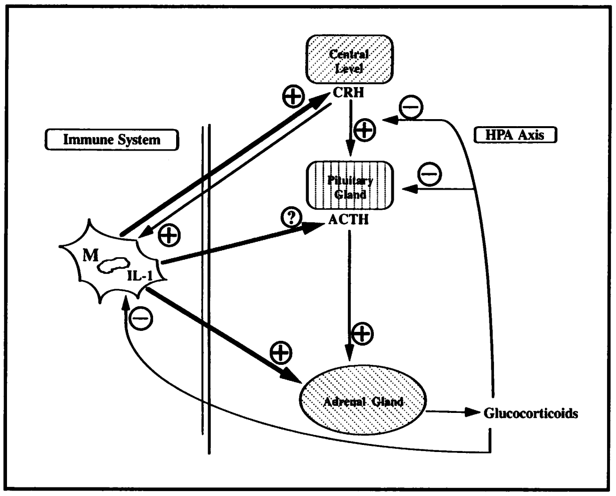

Figure 3.—The diagram represents the interaction between interleukin-1 (IL-1) and the hypothalamic-pituitary-adrenal (HPA) axis. ACTH = adrenocorticotropin hormone (corticotropin), CRH = corticotropin-releasing hormone, M = macrophages, ➡ = effects produced by IL-1 on hormonal regulation, → = effects produced by hormones on IL-1 regulation, + = stimulatory effect, − = inhibitory effect, ? = unknown

lease. The end point of all of these mechanisms is the IL-1-mediated increase of glucocorticoids by the HPA axis.[54]

There is evidence that glucocorticoids participate in a feedback loop with the IL-1 system and the HPA axis itself and exert an adverse effect on the immune system. Glucocorticoids inhibit IL-1-induced CRH release[55] and corticotropin production at the pituitary level.[54] Also, glucocorticoids inhibit the production or secretion of IL-1 in peritoneal macrophages[56] and specifically in cells present at the locus of inflammation. Therefore, it seems that IL-1 activates the HPA axis to elevate circulating glucocorticoid levels when an immunogenic challenge is presented, and glucocorticoids, in turn, inhibit excessive activation of the HPA axis and modulate many immune activities including IL-1 secretion. Also, glucocorticoids have inhibitory effects on inflammatory loci to reduce locally the production or secretion of cytokines. Once activated, cytokines could be highly toxic if they are not properly modulated. Such a regulatory circuit might explain the abnormal process of some diseases with an immune pathogenesis such as human cyclic neutropenia, Hashimoto's thyroiditis, and Lyme disease.[55]

Interactions Between the Interleukin-1 System and the Hypothalamic-Pituitary-Thyroid Axis

Thyroid disease not only occurs more commonly in women but also interferes with the reproductive function. It is well known that serum thyroid hormone levels change in severe illness, and thyroid dysfunction has been linked to reproductive failure through either anovulation or pregnancy wastage. Such abnormality is called "euthyroid sick syndrome" and is thought to be mediated, at least in part, by the effects of cytokines on the hypothalamic-pituitary-thyroid axis. The subcutaneous administration of IL-1β decreases plasma thyroid hormone and thyroid-stimulating hormone (TSH) levels in rats.[57] The inhibitory effect is not only at the pituitary level but also on the thyroid independent of TSH levels.[58] Direct action of IL-1 on thyroid cells has been shown with in vitro experiments. A small amount of IL-1 enhances thyroglobulin mRNA transcription, thyroglobulin secretion, and iodide organification induced by TSH, but larger doses suppress them.[59] Finally, the observation that IL-1 enhances the biosynthesis of somatostatin, a TSH release-inhibiting factor, in cultured hypothalamic neurons[60] suggests again that the hypothalamus is one of the sites of IL-1 action.

In summary, IL-1 inhibits the hypothalamic-pituitary-thyroid axis, acting at different levels. This cytokine acts at the level of the hypothalamus and pituitary to inhibit TSH secretion. Also, IL-1 inhibits the biosynthesis and release of thyroid hormone and thyroid cell growth, especially at large doses. The direct inhibitory action of this cytokine on the hypothalamus-pituitary-thyroid axis and the influence of the axis in reproduction may help to explain the pathogenesis of autoimmune hypothyroid disorders and their deleterious effects on reproduction.

Conclusion

Over the past decade, cytokines have become of increasing interest to reproductive scientists and clinicians. The function and actions of IL-1 are perhaps the best documented of all the cytokines in the area of reproduction. In this monograph, we have reviewed evidence of the relationship between the immune system and the reproductive endocrine system and the role of IL-1 in this interaction. It is well known that normal reproductive function relies on correct function and interaction among the hypothalamic-pituitary-gonadal, the hypothalamic-pituitary-adrenal, and the hypothalamic-pituitary-thyroid axes. Hence, we have reviewed the interactions between the IL-1 system and these three axes as well as the role of the IL-1 system in the ovary. Little is known of the presence and regulation of IL-1 receptors, and less is known about the interaction of IL-1 and its receptor with IL-1 receptor antagonist in the female reproductive system. Also, the actions of this cytokine may be different in different cell types (pleiotropy) or within different endocrine environments. More time and effort are required to learn about the interactions between the cytokine IL-1 and the reproductive system to fully understand processes such as ovulation and luteinization. Another area where IL-1 appears to be relevant in human reproduction, but was not reviewed here, is at the level of trophoblast-endometrial interaction. This field, which has recently emerged, has profound implications in fetal immune recognition leading to successful implantation and promises to generate exciting new concepts in reproductive immunology.

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